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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,159	02/27/2004	Takahiro Ochiya	082368-000200US	8186

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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	**PAPER NUMBER**
1651	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,159	OCHIYA ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/2/04, 7/11/05, 1/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-15 are currently pending.

Election/Restrictions

Applicant's election without traverse of the species "a first medium comprising retinoic acid and leukemia inhibitory factor; a second medium comprising acidic fibroblast growth factor; and a third medium comprising oncostatin M," "human," and "mesenchymal stem cells" in the reply filed on 2/9/07 is acknowledged.

Specification

The abstract of the disclosure is objected to because it comprises more than a single paragraph, and the first paragraph contains phrases that can be implied, *e.g.*, "The object of the present invention is...". Correction is required. See MPEP § 608.01(b) for guidance as to the content, format, and language of an abstract.

Drawings

The drawings are objected to because the photographs in Figures 3, 5-7, 11-15, 17, and 18 are dark and unintelligible. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several

views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing differentiation of a few types of pluripotent cells to hepatocytes using the claimed media, does not reasonably provide enablement for differentiating every pluripotent cell to every end point using these media. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in

the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

Independent claim 1 is drawn to a method of differentiating pluripotent cells by culturing them first in a culture media comprising acidic fibroblast growth factor (aFGF or FGF-1), FGF-4, and hepatocyte growth factor (HGF), hereafter "Medium 2"; and culturing them in another medium comprising oncostatin M (OSM), hereafter "Medium 3." Independent claim 4 is drawn to a method of differentiating pluripotent cells by culturing them in a culture media comprising retinoic acid (RA) and leukemia inhibitory factor (LIF), hereafter "Medium 1"; and culturing them in Medium 2. Independent claim 6 is drawn to a method of differentiating pluripotent cells by culturing them in Medium 1, in Medium 2, and in Medium 3. Independent claim 11 is drawn to a method of differentiating pluripotent cells to hepatocytes either by culturing them in Medium 2 and in Medium 3 or by culturing them in Medium 1, in Medium 2, and in Medium 3. Claims 2, 3, 5, and 7 limit the culture surfaces employed in each method. Claims 8-10, 13, and 14 limit the source of the pluripotent cells. Claim 12 requires that the differentiation in claim 11 be complete and yield mature hepatocytes. Claim 15 is limited to a method of differentiating mesenchymal stem cells (MSCs) to hepatocytes either by culturing them in Medium 2 and in Medium 3 or by culturing them in Medium 1, in Medium 2, and in Medium 3.

The specification provides one example (see page 33 *et seq.*) in which human MSCs are differentiated to hepatocytes by culturing them first in Medium 2 (comprising 200ng HGF, 300ng aFGF, and 60ng FGF4 per mL) and then in Medium 3 (comprising 10 mg OSM per mL) and another example (see page 19 *et seq.*) in which embryonic stem cells (ES cells) are differentiated to hepatocytes by culturing them first in Medium 1 (comprising 1000U LIF/mL and $1.0x10^{-8}$ M RA), then in Medium 2 (comprising undisclosed amounts of HGF, aFGF, and FGF4; see page 23, lines 31-32)and finally in Medium 3 (comprising an undisclosed amount of OSM; see page 23, line 24). However, the specification in view of the art lacks any teaching that the instantly claimed culturing steps can yield any mature cell type other than hepatocytes, *e.g.* a method for differentiating MSCs to neurons using Media 1, 2, and 3. The specification in view of the art also does not enable methods for transdifferentiating pluripotent cells that do not naturally differentiate to hepatocytes into hepatocytes, *e.g.* a method for transdifferentiating hematopoietic stem cells to hepatocytes using Media 1, 2, and 3.

Transdifferentation of pluripotent stem or progenitor cells to other cell types is a highly unpredictable art, despite the extremely high level of ordinary skill among cell biologists (*i.e.*, the postdoctoral level). Castro et al. (2002, *Science* 297: 1299; reference U) teach that bone marrow stem cells do not transdifferentiate into neural cells *in vivo*; however, subsequent communications in *Science* indicate that skilled artisans have not reached consensus as to the transdifferentiation potential of bone marrow cells (see Mezey et al. and Castro et al., *Science* 299: 1184b-c; reference V). Reinecke et al.

(2002, *J Mol Cell Cardiol* 34: 241-249; reference W) teach that skeletal muscle stem cells do not transdifferentiate into cardiomyocytes (Figure 2), but also point out that skilled artisans have not reached consensus as to the transdifferentiation potential of skeletal muscle stem cells (pages 245-247). Murry et al. (2004, *Nature* 428: 664-668; reference X) teach that bone marrow stem cells do not transdifferentiate into cardiac myocytes (Figures 1 and 2) but point out that skilled artisans have not reached consensus as to the transdifferentiation potential of bone marrow stem cells (page 667, column 2, paragraph 2). In short, the person of ordinary skill in the art would not have had a reasonable expectation at the time the invention was made that any particular stem cell type could transdifferentiate into any particular cell type without undue experimentation.

The claims (with the exception of claims 10 and 15) read on transdifferentiating pluripotent cells to diverse cell types (indeed, there is no claimed end point in claims 1, 4, and 6). Due to the unpredictable nature of the transdifferentiation art as demonstrated above, undue experimentation would have been required by the skilled artisan at the time of the invention to optimize the instantly claimed methods (which include no concentrations of growth factors or time in culturing steps) to differentiate each and every pluripotent cell to each and every mature cell type.

Similarly, the working examples in the specification are limited to differentiating MSCs and ES cells to hepatocytes; no specific guidance for differentiating these pluripotent cells to any other mature cell type is provided. Due to the unpredictable nature of the transdifferentiation art as demonstrated above, undue experimentation

would have been required by the skilled artisan at the time of the invention to optimize the instantly claimed methods (which include no concentrations of growth factors or time in culturing steps) to differentiate ES cells and MSCs to each and every mature cell type.

Furthermore, the data provided in Example 5 (see bottom of page 24) indicates that the choice of culture substrate dramatically affects the yield of hepatocytes from ES cells; depending on culture substrate, the method has a success rate between 2% and 38% (page 25, lines 1-5). Beyond trial and error, the specification provides no guidance for selecting the appropriate substrate to differentiate ES cells or MSCs to any given end point (other than hepatocytes).

Finally, it is noted for the record that the instant independent claims are drawn to methods comprising steps that are not claimed as being performed in any particular order. For example, claim 1 reads on a method of differentiating pluripotent cells by culturing them first in Medium 2 and then in Medium 3 **and** on a method of differentiating pluripotent cells by culturing them first in Medium 3 and then in Medium 2. The specification provides no evidence that the order of the steps may be reversed, and in light of the unpredictability of the transdifferentiation art, the skilled artisan wound require undue experimentation to determine whether the order of steps is essential for each and every differentiation process.

As discussed above, applicants present a narrow working embodiment in which ES cells and MSCs are differentiated to albumin-expressing cells (*i.e.*, hepatocytes) by culturing them in Media 1, 2, and 3, each of which comprises a particular amount of

each of its components. While a singular, narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the lack of direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4, and 6 refer to a medium "comprising any **one** of the following growth factors (i) to (iii)," but each of "(i)," "(ii)," and "(iii)" in these claims comprises more than one growth factor. Clarification is required. In the interest of compact prosecution, these limitations have been interpreted as being drawn to a medium "comprising a combination of growth factors selected from the group consisting of (i) aFGF, FGF-4, and HGF; (ii) aFGF and growth factors selected from the group consisting of activin A, EGF, and β-NGF; and (iii) FGF and growth factors selected from the group consisting of activin A and HGF."

Because claims 2, 3, 5, and 7-15 depend from indefinite claims 1, 4, and 6 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claims 2, 3, 5, and 7 require that variously coated dishes be "used" in the steps, but the verb "used" does not particularly describe the manner in which the dishes relate to the process. Clarification is required. In the interest of compact prosecution, and in light of the specification, these claims have been interpreted, for example, as reading "wherein the cells are cultured on a gelatin-coated culture dish in step (a)."

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-10 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. These claims do not recite any end point for the differentiation method; therefore, the process has no claimed product and no utility. The steps of the method *per se* are not useful unless they result in a useful product.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3 and 11-15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 11/210,337, which shares inventors and assignees with the instant application. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the claims in the '337 application are completely encompassed by the scope of the instant claims, i.e. they anticipate the instant claims.

Instant claim 1 is drawn to a method of differentiating pluripotent cells (of any type) to any end point comprising culturing the cells in a first medium comprising either aFGF, FGF4, and NGF; aFGF and either activin A, EGF, or b-NGF; or FGF4 and either activin A or HGF; and then culturing the cells in a second medium comprising oncostatin M. Claim 1 of the '337 application is a narrower embodiment of instant claim 1 in which the pluripotent cells are narrowed to human undifferentiated cells; the end point is narrowed to hepatocyte-like cells; the culturing step is carried out over a particular time; and an additional step of culturing in a medium comprising dexamethasone is added. Because the method in instant claim 1 **comprises** two steps, it encompasses any method that includes at least those two steps. See M.P.E.P. § 2111.03. Instant claim 2 encompasses claim 2 of the '337 application. Instant claim 10 encompasses claim 3 of the '337 application. Instant claims 11-15 are narrower versions of instant claim 1 in

which the starting material and/or end point for the method is particularly pointed out and, therefore, overlap in scope with claims 1-3 of the '337 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lora E Barnhart